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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,853	04/18/2005	Gilda De Luca	206,953	3983

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,853	DE LUCA ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,34-45,55-75 and 79-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31, 34-45, 55-75 and 79-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 12/08/2009 has been received, entered and carefully considered. The following information has been made of record in the instant amendment:

1. Claims 32-33, 46-54, 76-78 have been canceled.

2. New Claims 80-86 have been added.

3. Claims 37-38, 55, 58-59, 68, 70 and 79 have been amended.

4. Remarks drawn to rejections under 35 USC 103

The status of claims 80-86 and 37-38, 55, 58-59, 68, 70 and 79 indicated in the instant filing is the same as the status indicated for these claims in the RCE filed 3/17/2009.

Claims 1-31, 34-45, 55-75 and 79-86 are pending in the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 1-31, 34-45, 55-75 and 79-86 under 35 U.S.C. 103(a) as being unpatentable over Luo et al (Bioconjugate Chem. 1999, 10, 755-763; of record) in view of Sparer et al (Controlled Release Delivery Systems, Chapter 6, 1983, 107-119; of record), Li et al (US 5,977,163; of record), Desai et al (US 5,648,506; of record) and is reiterated below.

Luo et al, drawn to bioconjugates, teach conjugates of hyaluronic acid wherein the carboxyl group of the hyaluronic acid is covalently bonded to a linker via an amide linkage to Taxol (Figure 2, page 756). Such conjugates showed selective toxicity towards human cancer cell lines that overexpress hyaluronic acid receptors like CD44 and RHAMM and the conjugates showed no toxicity (page 755, abstract, right column, last paragraph). In addition to this, conjugation of anticancer and antitumor drugs to biopolymers provides advantages in drug stabilization, solubilization, localization and controlled release (page 756, right column, below figure 4).

In Figure 2 (page 756), Luo teaches the process for attachment of Taxol to hyaluronic acid wherein the carboxyl of the hyaluronic acid is attached to the spacer via an amide linkage on one end and the other end of the spacer is attached to the hydroxyl of the Taxol via an ester bond.

However, the conjugate of Luo comprises hyaluronic acid conjugated to Taxol via a spacer that is a dihydrazide, which is excluded by the proviso in instant claim 1. But one of skill in the art reading Luo's teaching will realize the importance of the conjugate of Taxol and hyaluronic acid since Luo teaches that in addition to advantages with respect to drug stabilization, solubilization and controlled release of the conjugated drug, it has the advantage of hyaluronic acid as the carrier, which is immunoneutral, biocompatible and biodegradable and has been used as a vehicle and angiostatic agent in cancer therapy (page 755, introduction). Moreover, CD44 and RHAMM that are overexpressed in cancer cells are receptors for hyaluronic acid (page 756, right column, see text below figure 4). This means that a conjugate of Taxol (Taxol shows activity against several cancers) and hyaluronic acid, which is biocompatible and has antiinflammtory properties, will show selectivity towards cancer cells and thus would have optimal beneficial effects.

Sparer et al, drawn to polysaccharide-drug complexes, teaches glycosaminoglycans including hyaluronic acid are drug carriers because of their favorable properties and have various functional groups available for forming different types of bonds with drugs (page 108, line 1 through page 109, line 3). Sparer reports especially the performance of amide and ester linked glycosaminoglycan drug complexes (page 109, 4-7), which are prepared via standard coupling reaction of the carboxyl group of the hyaluronic acid to the hydroxyl and the amino group of the drug (page 112). The

process for the formation of an ester linkage involves activation of the hydroxyl by dicyclohexyl carbodiimide (page 109, Experimental and page 110, last paragraph).

According to Sparer's study the release rate from amide complexes was slower and gave a prolonged constant release of the drug. According to Sparer, it would be ideal to obtain zero order release rate in all cases and still be able to vary the rate of release to fit the dosage regimen and this may be possible by selecting a given polymer drug bond and that his studies provide a base from which to design a drug release system. The rate of release may in principle be engineered by the judicious choice of drug-glycosaminoglycan bond based on the hydrolytic stability of the bond (page 117, last paragraph). This means that drug-glycosaminoglycan complexes containing bonds other than amide and ester may be important in controlled release and should be made and studied with respect to their hydrolysis. Even though Sparer does not teach a complex of glycosaminoglycans with Taxol, one of skill in the art will recognize from his teaching that the same could be done using hyaluronic acid and Taxol since both have several functional groups and different types of bonds could be formed between the two molecules with and without a spacer.

However, Luo and Sparer do not teach taxane conjugates, compositions, medical devices coated with the taxane compositions and a method of treating auto immune diseases as instantly claimed.

Li et al, drawn to Taxol complexes, teaches water-soluble complexes of paclitaxel and docetaxel with polyethylene glycol polymers (col. 1, lines 5-14). Their complexes are effective against cancers (col. 5, lines 13-18) and arthritis (col. 5, lines 43-65), and also useful for inhibiting restenosis and coating medical devices like stents (col. 5, line 66

through col. 6, line 43). According to Li such complexes improve the efficacy of anticancer therapy by providing water-soluble and controlled release paclitaxel derived compositions and also eliminate the need for solvents that are associated with side effects (col. 8, lines 34-41). The complexes could be made into compositions comprising excipients and diluents and can be made for different forms of administration. Specific antibacterial and antifungal agents could be added for preservation against microorganisms (col. 10, line 1 through 66). However, Li et al do not teach Taxol hyaluronic acid complexes. But from their teaching one of skill in the art would recognize the use of such complexes in a method of treatment of cancers, tumors and restenosis and for coating medical devices.

Desai, drawn to Taxol-carrier conjugates, teaches a process for the attachment of Taxol to carriers via different types of covalent linkages like ester, urethane, amide, amine and ether etc. (col. 4, lines 19-36 and examples 1-5). Even though Desai et al do not exemplify such conjugates using Taxol and hyaluronic acid as instantly claimed, one of skill in the art will recognize from the teaching of Desai and that of Sparer that the same type of process steps can be used for making Taxol-hyaluronic acid conjugates comprising different types of linkages as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a taxane covalently bonded to hyaluronic acid optionally using a spacer, and use them in a method of treatment and as a coating for medical devices since closely analogous complexes comprising the active agents and their use in treating cancer, restenosis and as coating for medical devices is seen to be taught in the

prior art. One of ordinary skill in the art would also use different spacers in order to look for optimal beneficial effects.

One of skill in the art would be motivated to make the complexes as instantly claimed via the process as instantly claimed and use them in a method of treatment as instantly claimed and in coating medical devices since Taxol and hyaluronic acid have many functional groups which makes it possible to make complexes via different type of bonds, which according to Sparer could lead to drug complexes with varied release times, which in turn would extend the duration of treatment. Complexation with hyaluronic acid has the advantage of biocompatibility and also selectivity to cancer cells because of the overexpression of receptors (CD44) of hyaluronic acid by these cells. The presence of several functional groups in both the agents also helps to make different types of bonds that link both the agents to each other with and without a spacer.

Response to Applicants Arguments

Applicants have traversed the rejection of record above arguing that:

1. Luo et al, at page 761, discloses the cytotoxicity results for four different cell lines. It is clear from these results that the best cytotoxicity of HA-ADH-Taxol (ADH is adipic dihydrazide) is against the human colon cancer cell line HCT-116. This is the reason Luo selected this cell line for further investigation. The instant inventors, wishing to make apparent unexpected results achieved by the conjugates of the claimed invention found it appropriate to provide a comparison between the claimed conjugates and the HA-ADH-Taxol conjugate of Luo using the same cell line. The claimed conjugates act better than free Taxol and also the known conjugate HA-ADH-Taxol.

2. Luo et al teach away from considering the disclosed conjugate typology.

3. Irrespective of the type of linkage and the mechanism of Taxol release Luo's conjugates have been shown to be worse that free Taxol. One of ordinary skill in the art would not ascribe the unsatisfactory results to the presence of the ester bond and hence would not go in that direction.

4. Luo teaches that high Taxol loading decreases the HA-Taxol solubility and thus limits the cytotoxicity of the conjugate relative to that of the free drug. This comment of Luo refers to preparations 1, 3, 7 and 8 in Table-2 of Luo. This means that cytotoxicity depends on a balance between minimal hyaluronic acid modification and maximal Taxol loading. According to Luo HA must have low molecular weight.

5. Sparer deals with drug-Glycosaminoglycan (GAG) complexes. There is no specific teaching of Hyaluronic acid and Taxol.

6. Li is drawn to paclitaxel and docetaxel complexes with polyethylene glycol polymers and Desai refers to Taxol complexes with polyethylene glycols.

Applicants' arguments have been considered but are not found to be persuasive.

Luo also teaches that their results support the notion that increased cytotoxicity of HA-Taxol conjugate requires cellular uptake of the complex followed by hydrolytic release of the active Taxol by cleavage of the labile 2'-ester linkage (page 761, right column, see second full paragraph). The Taxol-HA conjugate shown in Figure 2 of Luo (page 756) has an ester linkage on the side of the spacer bound to the Taxol. Luo's compounds have an adipic dihydrazide spacer which links Taxol to the hyaluronic acid (HA-ADH-Taxol). Luo also teaches that his HA-Taxol conjugate showed lower IC_{50}

compared to free Taxol. This means that there is not sufficient cellular uptake of the Taxol-HA conjugate of Luo. This suggests to one of ordinary skill in the art that to look for HA-Taxol conjugates with spacers other than hydrazide. Taxol is a well known cancer drug. According to Luo hyaluronic acid is an important signal for activating kinase pathways and regulating angiogenesis in tumors (Luo page 755, right column, bottom) and targeting of anti cancer agents to tumor cells can be accomplished by receptor mediated uptake of bioconjugates of anti-cancer agents to hyaluronic acid (page 756, right column, below Fig. 4). Hyaluronic acid (HA) receptors are expressed in cancer cells. From this teaching it is evident that one of ordinary skill in the art will consider conjugating HA to Taxol. Since the hydrazide in Luo's conjugate (spacer) did not yield encouraging results, one of ordinary skill in the art would look for Taxol-HA conjugates with other spacers that may show better activity than free Taxol.

One would also look for other types of linkages (based on the teaching of the secondary references, Sparer and Desai) that may be better than the ester linkage suggested by Luo.

Luo just states that low molecular weight hyaluronic acid can be cleared by the kidney. Even though Luo has used hyaluronic acid with a molecular weight of about 12,000, there is no teaching of the molecular weight cutoff for this clearance. This means that the artisan can vary the molecular weight for optimization purposes. According to Luo's teaching (page 761, right column, last paragraph though page 762 right column) cytotoxicity depends on a balance between minimal hyaluronic acid modification and maximal Taxol loading. This is a suggestion for adjustment of the percentage of Taxol loading. Since Luo teaches the need for a balance between balance between minimal

hyaluronic acid modification and maximal Taxol loading, one of ordinary skill in the art would adjust both these parameters for optimization. Luo does not establish any clear limitations regarding these parameters other than making a general statement regarding the balance between the two.

Sparer, Li and Desai teach are al relevant in that they teach drug release studies form conjugates (Sparer refers to conjugates of glycosaminoglycans, one of which is hyaluronic acid. Hyaluronic acid-HA, is used in the instant conjugate and is also used by Luo), Taxol conjugates having different linkages and the use of related Taxol conjugates for coating medical devices. Since Luo teaches the use of closely related Taxol conjugates and their anticancer activities, the secondary references need not teach or suggest the same. The skilled artisan can take the suggestion in the secondary references and apply them to Luo's teaching for modification purposes. This is well within the skill level of the artisan. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988 and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Teaching, suggestion and motivation along with a reasonable expectation of success for the instant invention is seen in the prior art.

Conclusion

Claims 1-31, 34-45, 55-75 and 79-86 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623